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Research article

Efficacy and safety of *Tongxin* formula in the treatment of coronary microvascular disease: A randomized, double-blind, placebo-controlled clinical trial study

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ABSTRACT

Objective: The objective of this study was to evaluate the efficacy and safety of *Tongxin* Formula in the treatment of coronary microvascular disease.

Methods: We conducted a randomized, double-blind, placebo-controlled study simultaneously in two hospitals, consisting of 80 participants. Using a random number table, we assigned patients to the treatment and control groups. Patients in both groups received conventional Western medicine for coronary microvascular disease. In addition, those in the treatment group received *Tongxin* formula granules, while those in the control group received a placebo. The treatment course for both groups was three months, and the follow-up duration was six months. The primary efficacy indicators were coronary blood flow reserve and cardiovascular adverse events; the secondary efficacy indicators were the traditional Chinese medicine (TCM) syndrome score, the angina symptom score, the Seattle Angina Questionnaire (SAQ) score, left ventricular function, and adverse reactions.

Results: After treatment, patients in the treatment group showed significantly higher variation in the coronary flow reserve (CFR) levels (CFR >2) and improvement of diastolic function (peak filling rate, or PFR >2.5) than those in the control group ($P < 0.05$). After 6 months of follow-up, the incidence of cardiovascular events in the treatment group was significantly lower than that in the control group ($P < 0.05$). After 3 months of treatment and 6 months of follow-up, the total effective rates of TCM symptoms and angina symptoms, as well as the total SAQ standard scores, in the treatment group were higher than those in the control group ($P < 0.05$). There were no serious adverse reactions in either group before or after treatment, and there was no significant change ($P > 0.05$).

Conclusion: We found that *Tongxin* Formula combined with conventional Western medicine can significantly improved the level of coronary blood flow reserve, reduced the occurrence of cardiovascular adverse events, improved the clinical symptoms of patients, and enhanced the quality of life of patients with coronary microvascular disease with favorable safety.

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1. Introduction

Subepicardial coronary stenosis is a type of coronary microvascular disease (CMVD) [1,2]. Despite advances in coronary revascularization technology (coronary stenting, coronary bypass grafting, etc.), some patients still experience angina symptoms or clinical manifestations of angina despite normal coronary angiography. CMVD is a clinical syndrome with objective evidence of exertional angina or myocardial ischemia characterized by structural and/or functional abnormalities of the anterior coronary arterioles (0.1–0.5 mm) and arterioles (0.1 mm) with the involvement of multiple causative factors [3]. The initial focus was on the large vessels of the coronary artery, but not much was known about the structure and function of coronary microcirculation. Moreover, CMVD was thought to have a good prognosis. Recent research, however, has shown that CMVD is on the rise, and with it comes an increased risk of severe cardiovascular events [4].

The present examination and treatment approaches, however, focus mainly on large coronary artery vessels. Coronary microvessels cannot be directly observed using coronary angiography, and the functional status of coronary microvessels is indirectly assessed mainly by coronary blood flow. Abnormalities in coronary microcirculation can lead to impaired coronary blood flow response to vasodilation stimuli, characterized by diminished coronary flow reserve (CFR) (CFR <2.0–2.5) or abnormally high index of microvascular resistance (IMR) (IMR >25) and/or focal or diffuse vasoconstriction during acetylcholine provocation testing, as well as the absence of any significant epicardial coronary artery occlusion (>50 % lumen stenosis during coronary angiography) or fractional flow reserve (FFR >0.80) [5,6].

In CMVD without obstructive epicardial coronary artery disease, the decline in CFR denotes the presence of CMVD. Murthy et al. estimated that CFR <1.5 increased the risk of cardiac death by 16 times, and CFR between 1.5 and 2.0 increased the risk of cardiac death by 5.7 times [7]. CFR <2 is considered an independent predictor of adverse cardiovascular events [8]. Therefore, CFR has substantial clinical significance for the early detection of CMVD and the evaluation of therapeutic effects. Despite decades of academic and clinical study on CMVD, many questions remain unanswered, including the disease's pathogenesis, limited diagnostic techniques, and unclear long-term efficacy.

Although CMVD is not specifically named in traditional Chinese medicine (TCM), it can be classified as "chest obstruction" based on its clinical symptoms. There have been several useful studies on the prevention and treatment of CMVD. Previous studies focused on starting treatment from the liver and kidney, the disharmony of collaterals, and the theory of "collateral deficiency and wind movement", or with the use of the spleen-regulation-and-heart-protection method, aromatic warm and smooth theory, weak yang meridian and stringy yin meridian theory, and so on [9–14]. With a foundation in the classics, treatment combines examination of symptoms, identification of causes, and therapy based on syndrome differentiation. This approach in TCM has been beneficial in offering new diagnostic and therapeutic ideas for the treatment of CMVD. However, there is a lack of high-quality clinical studies to provide study-based evidence. In the previous study, the research team found that Tongxin decoction can improve the vascular endothelial function of CHD miniature pigs, thereby promoting the increase of FGF and VEGF vascular growth factors, thus promoting the growth of collateral circulation of CHD miniature pigs [15]. In addition, Tongxin formula combined with conventional western medicine can stimulate the release of bone marrow endothelial progenitor cells to peripheral blood in patients with coronary heart disease, significantly increase the proliferation of endothelial progenitor cells in peripheral blood, and improve the clinical symptoms of patients [16]. Therefore, we designed a randomized, double-blind, placebo-controlled clinical trial to further observe the efficacy

Table 1
Comparison of general data.

Item	Treatment group (N = 37)	Control group (N = 38)	x^2/t/Z	*P*
Gender (N, %)			1.072	0.300
Male	17 (45.9 %)	22 (57.9)		
Female	20 (54.1 %)	16 (42.1)		
Age ($\bar{x}$ ±SD, years)	61.41 ± 12.573	64.87 ± 9.032	−0.955	0.340
Underlying diseases (N, %)				
PCI	26 (70.3 %)	25 (65.8 %)	0.173	0.677
CABG	1 (2.7 %)	4 (10.5 %)	0.801	0.371
Hypertension	23 (62.2 %)	19 (50 %)	1.125	0.289
Diabetes	15 (40.5 %)	14 (36.8 %)	0.108	0.742
Hyperlipidemia	17 (45.9 %)	13 (34.2 %)	1.076	0.300
Risk factors (N, %)				
History of smoking	14 (37.8 %)	18 (47.4 %)	0.696	0.404
History of alcohol consumption	16 (43.2 %)	19 (50 %)	0.344	0.558
Disease course ($\bar{x}$ ±SD, years)	2.78 ± 1.548	3.13 ± 1.545	−1.069	0.285
Basic medication (N, %)				
ACEI/ARB	28 (75.7 %)	32 (84.2 %)	0.853	0.356
β blockers	25 (67.6 %)	21 (55.3 %)	1.197	0.274
Calcium ion antagonist	20 (54.1 %)	25 (65.8 %)	1.076	0.300
Diuretic	8 (21.6 %)	11 (28.9 %)	0.532	0.466
Statins	36 (97.3 %)	35 (92.1 %)	0.237	0.627
Antiplatelet	33 (89.2 %)	34 (89.5 %)	0.000	1.000
Nitrates	22 (59.5 %)	25 (65.8 %)	0.321	0.571

Note: The χ^2 test and Wilcoxon rank sum test were used.

Table 2
Comparison of coronary blood flow reserve pre- and post-treatment between the two groups [M (P25,P75)].

Coronary branches	Treatment course	Control group	Treatment group	Z value	*P* value
LAD	Before treatment	1.83 (1.68, 2.06)	1.74 (1.52, 1.86)[a]	−2.38	0.017
	After treatment	1.94 (1.71, 2.18)[a]	2.57 (2.15, 3.36)*[a]	−5.278	<0.001
LCX	Before treatment	1.85 (1.65, 2.12)	1.83 (1.65, 1.95)	−0.816	0.414
	After treatment	2.03 (1.83, 2.30)[a]	2.68 (2.27, 2.97)*[a]	−5.252	<0.001
RCA	Before treatment	1.88 (1.76, 2.01)	1.83 (1.63,2.01)	−0.965	0.335
	After treatment	1.87 (1.70, 2.13)	2.65 (2.36, 3.51)*[a]	−6.259	<0.001
TOT	Before treatment	1.84 (1.73, 1.92)	1.83 (1.66, 1.92)	−0.509	0.611
	After treatment	2.02 (1.93, 2.13)[a]	2.64 (2.47, 3.05)*[a]	−6.508	<0.001

Note.
[a] : $P < 0.05$ compared with the control group of the same period; a: $P < 0.05$ compared with the same group before treatment.

and safety of Tongxin formula in the treatment of coronary microvascular disease, and to explore the possible mechanism of action of Tongxin formula in the treatment of coronary microvascular disease.

2. Materials and methods

2.1. Study respondents

We enrolled 80 patients undergoing treatment at the Department of Cardiology in the Shanghai Hospital of Traditional Chinese Medicine (n = 40) and the Shanghai Tenth People's Hospital (n = 40) between November 2019 and July 2022. Using the random number table method, we randomly assigned patients to the treatment and control groups, with 40 patients in each group. During the course of the study, 5 enrolled patients were lost to follow-up due to refusal to review or regular medication. Only 75 patients were included in the final analysis, including 37 in the treatment group and 38 in the control group. Five patients dropped out of the study; these included three cases in the treatment group and two cases in the control group, accounting for 6.25 % of the total. All 75 patients were followed up. There were no significant differences in gender, age, underlying diseases, risk factors, disease course, medication, or other factors between the two groups ($P \geq 0.274$), and the groups were clinically comparable (Table 1).

2.2. Diagnostic criteria

2.2.1. Diagnostic criteria of western medicine

We referred to the 2017 *Chinese Expert Consensus on the Diagnosis and Treatment of Coronary Microvascular Diseases* for the Western medical diagnostic criteria for CMVD: CMVD refers to a clinical syndrome with objective evidence of exertional angina pectoris or myocardial ischemia due to structural and/or functional abnormalities of the anterior coronary arterioles and arterioles with the involvement of multiple causative factors [3].

2.2.2. TCM diagnostic criteria

The diagnostic criteria for TCM qi deficiency and blood stasis symptoms of CMVD that we referred to for chest obstruction, qi deficiency, and blood stasis symptoms were from the *TCM Differentiation Standards for Coronary Heart Disease* and the 2002 *Guidelines for Clinical Research of New Chinese Medicines* [17,18]. The main symptoms include: (1) chest pain; and (2) chest tightness. Secondary symptoms include: (1) palpitations; (2) shortness of breath; (3) fatigue; (4) a dark-purple complexion; (5) a dark-purple tongue with ecchymosis and petechiae; (6) a thin white coating on the tongue; and (7) stringy and unsmooth pulses. Diagnosis requires the presence of one of the main symptoms, one of the secondary symptoms of (1)–(3), and one of the secondary symptoms of (4)–(7).

Table 3
Comparison of post-treatment coronary blood flow reserve between the two groups.

Coronary branches	Group	Total (n)	CFR<2 [n (%)]	CFR>2 [n (%)]	X^2	*P* value
LAD	Control group	37	1 (2.7)	36 (97.3)	23.181	<0.001
	Treatment group	38	20 (52.6)	18 (47.4)		
LCX	Control group	37	2 (5.4)	35 (94.6)	27.607	<0.001
	Treatment group	38	24 (63.2)	14 (36.8)		
RCA	Control group	37	2 (5.4)	35 (94.6)	16.881	<0.001
	Treatment group	38	18 (47.4)	20 (52.6)		
TOT	Control group	37	1 (2.7)	36 (97.3)	18.159	<0.001
	Treatment group	38	17 (44.7)	21 (55.3)		

Note: The χ^2 test was used.

Table 4
Comparison of the number of patients with unstable angina and repeated hospitalizations between the two groups.

Category	Group	Case	Number of patients with case occurrences [N (%)]	Number of patients without case occurrences [N (%)]	X^2	*P*
Unstable angina	Treatment group	37	5 (13.5)	32 (86.5)	7.602	0.006
	Control group	38	16 (42.1)	22 (57.9)		
Repeated hospitalizations	Treatment group	37	6 (16.2)	31 (83.8)	7.173	0.007
	Control group	38	17 (44.7)	21 (55.3)		

Note: The χ^2 test was used.

2.3. Inclusion criteria

(1) Patients with myocardial ischemia symptoms, such as exertional or resting angina; (2) patients with CFR <2 in D-SPECT evaluation; (3) patients in whom coronary angiography or CT confirmed no coronary stenosis greater than 50 %; (4) patients aged 40–80 years old, male or female; (5) patients who were diagnosed with qi deficiency and blood stasis as per TCM criteria; and (6) patients and their families who were willing to participate in the study.

2.4. Exclusion criteria

(1) Patients with grade 3–4 cardiac function or pulmonary edema; (2) patients with severe primary cerebral or pulmonary diseases or liver and kidney insufficiency; (3) patients who were allergic to TCM medicines; (4) patients with malignant diseases; (5) patients with severe inflammatory diseases; (6) patients with bleeding disorders; (7) patients with malignant arrhythmia; (8) patients with acute coronary syndrome; (9) patients with critical and severe hypertension; (10) patients with psychiatric illnesses; (11) pregnant or lactating women; and (12) patients who participated in other clinical trials within one month prior to this study.

2.5. Termination and withdrawal criteria

(1) Unexpected events requiring discontinuation of the experimental drug treatment (including intolerance to the experimental drug); (2) patients with deteriorating conditions who were unable to take the experimental drug again; (3) patients who refused to continue participating in the study; (4) patients who, in the researcher's opinion, were considered unfit to participate in the trial; (5) patients who violated the research protocol (including poor compliance).

Table 5
Comparison of TCM syndrome scores and total scores[M(P_{25},P_{75})].

TCM symptoms	Treatment course	Control group	Treatment group	Z value	*P* value
Chest distress	Before treatment	4 (4,6)	4 (4,4)	1.897	0.058
	3 months of treatment	4 (2,4)[a]	2 (2,2)*[a]	4.589	<0.001
	6 months of follow-up	2 (0,4)[ab]	0 (0,0)*[ab]	3.133	0.002
Chest pain	Before treatment	2 (2,4)	4 (2,4)	1.331	0.183
	3 months of treatment	2 (0,2)[a]	0 (0,2)*[a]	3.662	<0.001
	6 months of follow-up	0 (0,0)[ab]	0 (0,0)*[ab]	2.267	0.023
Palpitation	Before treatment	2 (2,3)	2 (2,3)	1.103	0.270
	3 months of treatment	2 (1,2)[a]	2 (2,2)*[a]	2.169	0.030
	6 months of follow-up	1 (1,2)[ab]	0 (0,1)*[ab]	4.422	<0.001
Shortness of breath	Before treatment	2 (2,3)	2 (2,3)	1.795	0.073
	3 months of treatment	2 (1,2)[a]	2 (2,2)*[a]	2.165	0.030
	6 months of follow-up	2 (1,2)[a]	1 (1,1)*[ab]	5.461	<0.001
Weariness	Before treatment	2 (1,2)	2 (1,2)	0.667	0.505
	3 months of treatment	2 (1,2)[a]	1 (1,2)*[a]	2.019	0.044
	6 months of follow-up	1.5 (1,2)[ab]	1 (1,1)*[ab]	4.587	<0.001
Cyanosis	Before treatment	1 (1,1)	1 (1,1)	0.791	0.429
	3 months of treatment	1 (1,1)	1 (1,1)*[a]	3.041	0.002
	6 months of follow-up	1 (1,1)[ab]	0 (0,0.5)*[ab]	6.435	<0.001
Total scores	Before treatment	15 (11.75,18.25)	15 (12.5,17)	0.298	0.766
	3 months of treatment	11 (9,13.25)[a]	8 (8,10)*[a]	3.547	<0.001
	6 months of follow-up	7.5 (5,10.25)[ab]	3 (2,4)*[ab]	5.228	<0.001

Note: * Compared with the control group in the same period, $P < 0.05$; a compared with the same group before treatment $P < 0.05$; b compared with the same group after 3 months of treatment $P < 0.05$.

Table 6
Comparison of the efficacy evaluation for TCM symptoms between the two groups.

Time	Group	Case (N)	Invalid [N (%)]	Valid [N (%)]	Significant effect	Efficacy (%)	X^2	*P*
3 months of treatment	Treatment group	37	9 (24.3)	28 (75.7)	0	75.7	18.273	<0.001
	Control group	38	28 (73.7)	10 (26.3)	0	26.3		
6 months of treatment	Treatment group	37	4 (10.8)	5 (13.5)	28 (75.7)	89.1	36.059	<0.001
	Control group	38	10 (26.3)	25 (65.8)	3 (7.9)	73.6		

Note: The χ^2 test was used.

Table 7
Comparison of symptom scores and total scores of angina pectoris [M(P_{25},P_{75})].

Symptoms of Angina pectoris	Treatment course	Control group	Treatment group	Statistical values	*P* value
Number of episodes	Before treatment	4 (2, 4)	4 (3, 6)	−1.094	0.274
	3 months of treatment	2 (2, 4)[a]	2 (2, 2)*[a]	−2.998	0.003
	6 months of follow-up	2 (2, 4)[a]	2 (0, 2)*[ab]	−5.089	<0.001
Duration	Before treatment	4 (2, 4.5)	4 (2, 6)	−0.056	0.955
	3 months of treatment	2 (2, 4)[a]	2 (2, 3)*[a]	−2.039	0.041
	6 months of follow-up	2 (2, 4)[ab]	2 (0, 2)*[ab]	−3.268	0.001
Degree of pain	Before treatment	2 (2, 4)	2 (2, 4)	−1.114	0.265
	3 months of treatment	2 (0, 4)[a]	2 (0, 2)*[a]	−2.822	0.005
	6 months of follow-up	2 (0, 2)[ab]	0 (0, 0)*[ab]	−3.159	0.002
Total scores	Before treatment	10 (7.5, 12.5)	12 (8, 14)	−0.999	0.318
	3 months of treatment	8 (5.5, 12)[a]	6 (4, 6)*[a]	−3.418	0.001
	6 months of follow-up	6 (4, 8.5)[ab]	2 (2, 4)*[ab]	−5.153	<0.001

Note: * Compared with the control group in the same period, $P < 0.05$; a compared with the same group before treatment $P < 0.05$; b compared with the same group after 3 months of treatment $P < 0.05$.

2.6. Treatments

As per the inclusion and exclusion criteria, we enrolled and randomly assigned 40 patients each to the treatment and control groups using the random number table method. Patients in both groups received conventional Western medicine drugs as the basic treatment. The conventional western medicine treatment here mainly includes: ACEI or ARB, beta-blockers, CCB, anti-platelet drugs (such as aspirin, clopidogrel), statins, etc. Medications were given for three months, and patients were followed up for six months.

Treatment group: Along with conventional Western medicine, patients received the *Tongxin* formula twice a day, one pack each time. The composition of the *Tongxin* formula was as follows: 30 g of astragalus; 12 g of ground beetle; 12 g of *Rhizoma chuanxiong*; 15 g of peach kernel; 15 g of *Rhizoma sparganii*; 12 g of cassia twig; and 15 g of the rhizome of Rehmannia. The drugs were in the form of granules, all of which were uniformly processed and manufactured by the Guangzhou YiFang Traditional Chinese Medicine Co., Ltd.

Control group: Along with conventional western medicine, patients in the control group received placebo granules, which containing 8 % active ingredient with the same in shape, color, size and taste as the treatment group., twice a day, one pack each time. The drugs were uniformly processed and manufactured by the Guangzhou YiFang Traditional Chinese Medicine Co., Ltd.

2.7. Observation indicators

2.7.1. Primary observation indicators

(1) Coronary flow reserve (CFR): adenosine stress dynamic myocardial perfusion imaging was performed with D-SPECT before treatment and three months after treatment to evaluate the blood flow reserve of the anterior descending coronary artery, the circumflex artery, and the right coronary artery. CFR <2 was considered abnormal. D-SPECT is mainly the use of radioactive isotopes as tracers (imaging agents), the tracer is injected into the patient's body, with the blood flow, in the myocardial aggregation, so that the myocardial becomes the source of gamma rays, the use of D-SPECT machine to detect the number of rays emitted by each large blood vessel of the heart. You know the distribution of the tracer in the heart muscle, and the amount of radioactivity that accumulates in each part of the heart muscle is related to the amount of blood flow that reaches that part.

Table 8
Comparison of efficacy evaluation for angina symptoms between the two groups.

Time	Group	Case (N)	Invalid [N (%)]	Valid [N (%)]	Significant effect	Efficacy (%)	X^2	*P*
3 months of treatment	Treatment group	37	1 (2.7)	13 (35.1)	23 (62.2)	97.3	29.737	<0.001
	Control group	38	16 (42.1)	19 (50)	3 (7.9)	57.9		
6 months of treatment	Treatment group	37	5 (13.5)	31 (83.8)	1 (2.7)	86.5	38.64	<0.001
	Control group	38	31 (81.6)	7 (18.4)	0 (0)	18.4		

Note: The χ^2 test was used.

Table 9
Comparison of SAQ standard scores between the two groups [M (IQR)].

Item	Treatment course	Control group	Treatment group	Statistical values	*P* value
Physical limitation (PL)	Before treatment	57.78 (11.11)	55.56 (8.89)	−1.561	0.119
	3 months of treatment	66.67 (13.33)[a]	77.78 (18.89)*[a]	−3.024	0.002
	6 months of follow-up	74.44 (18.89)[ab]	88.89 (10)*[ab]	−4.120	<0.001
Anginal stability (AS)	Before treatment	75 (25)	50 (25)	−1.592	0.111
	3 months of treatment	75 (25)[a]	100 (25)*[a]	−3.644	<0.001
	6 months of follow-up	100 (25)[ab]	100 (0)*[ab]	−2.834	0.005
Anginal frequency (AF)	Before treatment	60 (30)	50 (20)	−1.483	0.138
	3 months of treatment	70 (20)[a]	90 (10)*[a]	−5.044	<0.001
	6 months of follow-up	80 (20)[ab]	100 (10)*[ab]	−5.361	<0.001
Treatment satisfaction (TS)	Before treatment	64.71 (23.53)	70.59 (17.65)	−0.525	0.600
	3 months of treatment	76.47 (17.65)[a]	88.24 (17.65)*[a]	−3.297	0.001
	6 months of follow-up	88.24 (23.53)[ab]	100 (5.88)*[ab]	−3.182	0.001
Disease perception (DP)	Before treatment	66.67 (18.75)	58.33 (33.33)	−1.254	0.210
	3 months of treatment	75 (16.67)[a]	91.67 (33.33)*[a]	−2.984	0.003
	6 months of follow-up	83.33 (16.67)[ab]	100 (8.33)*[ab]	−4.165	<0.001
Total scores	Before treatment	322.43 (86.73)	279.05 (80.54)	−1.537	0.124
	3 months of treatment	373.19 (47.27)[a]	429.90 (77.48)*[a]	−4.949	<0.001
	6 months of follow-up	416.63 (59.54)[ab]	480.78 (33.38)*[ab]	−5.712	<0.001

Note: *: Compared with the control group of the same period, $P < 0.05$; [a]: compared with the same group before treatment $P < 0.05$; [b]: compared with the same group after 3 months of treatment $P < 0.05$.

Therefore, according to the amount of myocardial local radioactivity, the blood perfusion of the myocardium can be analyzed to determine whether there is myocardial ischemia.

(2) Follow-up of major cardiovascular events: major cardiovascular events within six months of follow-up, including the number of hospitalizations due to cardiovascular diseases, the degree of heart failure, acute myocardial infarction, unstable angina, severe arrhythmias, cardiac death, stroke, and so on.

2.7.2. Secondary observational indicators

(1) TCM symptom scores

All patients filled out the TCM Qi Deficiency and Blood Stasis Symptom Score Scale [18] before treatment, 3, and 6 months after treatment, which measures symptoms such as chest pain, chest tightness, palpitation, shortness of breath, fatigue, and so on, based on the 2002 *Guidelines for Clinical Research of New Chinese Medicines* [18].

Efficacy evaluation criteria for TCM syndrome were based on the TCM symptom score scale, and the efficacy index (n) = (pre-trial scores - post-trial scores)/pre-trial scores × 100 %

Clinically controlled: n ≥ 90 %; significant effect: 70 % ≤ n < 90 %; valid: n ≥ 30 % < 70 %; invalid: n < 30 %.

Efficacy evaluation criteria for a single TCM symptom were as follows:

Clinically controlled: disappearance of symptoms post-treatment;

Significant effect: symptoms decreased by two grades post-treatment as compared with pre-treatment.

Valid: symptoms decreased by one grade post-treatment as compared with pre-treatment;

Invalid: no change or worsening of symptoms post-treatment.

(2) Angina symptom scores

All patients filled out the Angina Symptom Score scale [19] before treatment, 3, and 6 months after treatment, which mainly includes the number of angina attacks, duration, and degree of pain.

Efficacy evaluation criteria for angina symptoms were based on the Angina Symptom Score, and the efficacy index (n) = (pre-trial scores - post-trial scores)/pre-trial scores × 100 %

Table 10
Comparison of pre- and post-treatment diastolic function between the two groups.

Treatment course	Group	Decreased diastolic function [N (%)]	Normal diastolic function [N (%)]	X^2	*P*
Before treatment	Treatment group (N = 37)	26 (70.3)	11 (29.7)	0.427	0.514
	Control group (N = 38)	24 (63.2)	14 (36.8)		
After treatment	Treatment group (N = 37)	10 (27.0)	27 (73.0)[a]	5.121	0.024
	Control group (N = 38)	20 (52.6)	18 (47.4)		

Note: Using the χ^2 test.

[a] : $P < 0.05$ compared with the control group of the same period.

Significant effect: n ≥ 70 %; Valid: 30 % ≤ n < 70 %; Invalid: 0 ≤ n < 30 %; Aggravation: n < 0.

(3) Seattle Angina Questionnaire score

All patients filled out the Seattle Angina Questionnaire (SAQ) [20–22] before treatment, 3, and 6 months after treatment. This tool for evaluating disease-specific health status consists of 19 questions and 5 health conditions related to coronary heart disease: frequency of angina, physical limitation, quality of life, stability of angina, and treatment satisfaction.

(4) Left ventricular function assessment

Static myocardial perfusion imaging scans were performed with D-SPECT before treatment and three months after treatment for quantitative analysis of left ventricular function. The measurements included the end-diastolic volume (EDV), end-systolic volume (ESV), left ventricular ejection fraction (LVEF), peak ejection rate (PER), and peak filling rate (PFR). The absolute values of PER and PFR <2.5 were considered as indicating decreased systolic or diastolic function.

(5) Safety indicators

Routine investigations for blood, urine, feces, liver and kidney function, electrolytes, blood glucose, blood lipids, and coagulation function were done before treatment and three months after treatment.

2.8. Statistical analysis

We used SPSS 26.0 for statistical analysis. Measurement data conforming to a normal distribution were expressed using the mean ± standard deviation ($\overline{X}$ ±SD), and measurement data that did not conform to a normal distribution were expressed using the median and percentile M (P25, P75) or the interquartile range [M (IQR)]. Counting data were expressed using the number of examples (percentage), or N (%). We used the *t*-test for comparing measurement data conforming to the normal distribution and homogeneity of variance; otherwise, we used the rank sum test. We used the χ^2 test for the comparison of counting data. $P < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Comparison of primary observation indicators

3.1.1. Comparison of coronary blood flow reserves

There were no significant differences in the baseline pre-treatment levels of the left circumflex (LCX), right coronary artery (RCA), and total (TOT) CFR between the two groups ($P > 0.05$). Post-treatment, there was a significant increase in the CFR levels in both groups (both $P < 0.05$). When compared to the control group, the post-treatment CFR level of the treatment group was significantly different ($P < 0.05$) (Tables 2 and 3).

3.1.2. Comparison of adverse cardiovascular events

There were no serious cardiovascular events such as severe heart failure (grade 4 cardiac function), myocardial infarction, severe arrhythmia, cerebrovascular accident, or cardiac death in either group during follow-up. In the treatment group, five patients had unstable angina, and six patients were repeatedly hospitalized due to aggravation of chest tightness and chest pain (hospitalizations ≥3). In the control group, 16 patients had unstable angina, and 17 patients were repeatedly hospitalized due to aggravation of chest tightness and chest pain. A comparison of the groups showed that these differences were significant (all $P < 0.05$) (Table 4).

3.2. Comparison of secondary observation indicators

3.2.1. Comparison of individual TCM symptom scores and TCM symptom efficacy

Pre-treatment, there was no significant difference in individual TCM symptom scores or total scores between the two groups ($P > 0.05$), and the groups were comparable. Post-treatment, the TCM symptom scores decreased significantly in both groups ($P < 0.05$). There were significant differences in TCM symptom efficacy in the treatment group after three months of treatment and six months of follow-up when compared with the control group ($P < 0.05$) (Tables 5 and 6).

3.2.2. Comparison of individual angina symptom scores and angina symptom efficacy

There was no significant difference in the pre-treatment scores for individual angina symptoms or the total scores between the two groups ($P > 0.05$), and the groups were comparable. Post-treatment, the angina symptom scores decreased in both groups, and the difference was statistically significant ($P < 0.05$). When compared with the control group, there were significant differences in the angina symptom efficacy in the treatment group after three months of treatment and six months of follow-up ($P < 0.05$) (Tables 7 and 8).

3.2.3. Comparison of the Seattle Angina questionnaire (SAQ) standard scores between both groups

There was no significant difference in the pre-treatment SAQ standard scores between the two groups ($P > 0.05$), which was comparable. Post-treatment, both the standard scores and total scores of the SAQ increased, and the pre- and post-treatment differences in the two groups were all significant (all $P < 0.05$). The SAQ standard scores of the treatment group after three months of treatment and six months of follow-up were significantly different when compared to the control group ($P < 0.05$) (Table 9).

3.3. Comparison of left ventricular function assessment

The left ventricle ESV, left ventricle EDV, LVEF, and PER were within the normal range in patients in the two groups pre- and post-treatment, with no significant changes ($P > 0.05$). The post-treatment PFR and diastolic function between the two groups were significantly different ($P < 0.05$) (Table 10).

3.4. Drug safety evaluation

During the clinical trial, safety indicators, including routine investigations of blood, urine, feces, liver and kidney function, electrolytes, blood lipids, blood glucose, and coagulation function, were done in both groups before and after treatment. The results showed that each indicator of the two groups was within the normal range pre- and post-treatment; no serious liver and kidney function impairment, drug allergy, or other serious adverse reactions were found; and there was no significant change before and after treatment ($P > 0.05$).

4. Discussion

Although research on CMVD has been carried out for several years, its pathogenesis remains unclear. Currently, it is considered to be more related to the structural abnormalities of microvessels, dysfunction, and other extravascular mechanisms. Furthermore, the small diameter of coronary microvessels makes it difficult to differentiate them with the existing imaging techniques. As a result, the diagnostic technology for coronary microvessels is limited in scope at present.

In a study involving 11,223 patients, it was found that patients with stable angina and normal or diffuse non-obstructive coronary artery diseases had increased risks of cardiovascular adverse events and all-cause mortality as compared with patients without ischemic heart diseases [4]. However, due to the unclear pathogenesis of CMVD, limited diagnostic techniques, and varied clinical symptoms of patients, the current treatment of CMVD typically begins with anti-atherosclerosis, anti-angina, anti-platelet aggregation, improvement of endothelial dysfunction, improvement of myocardial ischemia, and so on.

There are small studies showing that ranolazine, ivabradidine, nicorandil, and miberatil, among others, may offer therapeutic benefits for patients with CMVD [23,24], with nicorandil being the most researched drug. Nicorandil has been found to improve myocardial ischemia without changing cardiac autonomic activity, suggesting that it has a direct vasodilating effect on coronary microvessels in patients with CMVD [25]. However, there are no large randomized clinical trials involving patients with CMVD and considering cardiovascular events as observational endpoints. Thus, it is unclear which treatments reduce the occurrence of cardiovascular events in patients with CMVD.

In TCM, although there is no disease that directly corresponds to CMVD, it is classified as “chest obstruction" and “heartache" based on its typical characteristics of chest tightness and chest pain. The name chest obstruction originates in the *Huangdi Neijing*. Zhang Zhongjing of the Eastern Han Dynasty proposed naming the condition “chest obstruction" and authored an article exclusively on the disease and its treatment in the *Synopsis of Golden Chamber*. As described in the *Synopsis of Golden Chamber - Pulse, symptoms, and treatment of Chest obstruction, Heartache, and Short of Breath* [26,27].

However, based on the physiological and anatomical characteristics of CMVD, some scholars have classified these symptoms in the collateral disease category of TCM [28]. They consider that disharmony of collaterals is its pathological basis, phlegm-blood stasis is the core pathogenesis, and it is characterized by the evolution law of heat-transmission of cold and evil in the early stage, phlegm and stasis in the middle stage, and sthenia syndrome and asthenia syndrome in the later stage [29].

In short, CMVD has a complex pathogenesis that integrates multiple elements of origin, including *qi*, blood, collaterals, phlegm, and stasis. This is consistent with the Western medical understanding of the complex pathological process involving multiple interconnected factors.

At present, TCM treatment for CMVD involves methods such as invigorating *qi*, activating the blood, and dissolving phlegm, mainly using drugs such as astragalus, leech, *Rhizoma chuanxiong*, *Rhizoma sparganii*, *gualou*, *xiebai*, and so on [30–33]. Considering the characteristics of the complex pathogenesis of CMVD, our research group has condensed Tongxin formula through long-term clinical research.

The *Tongxin* formula was distilled after extensive clinical research. In the formula, astragalus is sweet in taste and warm in nature, which reinforces vital energy, tonifies *qi* to promote blood circulation, disperses stasis, and dredges the collaterals. Its effect may be related to the fact that Astragaloside, the main ingredient of astragalus can improve myocardial energy metabolism, inhibit myocardial remodeling and oxidative stress damage, as well as promote angiogenesis [34–37]. Ground beetle, *Rhizoma chuanxiong*, peach kernel, and *Rhizoma sparganii* activate blood and remove stasis, and when used in combination, can dissolve stasis and promote blood circulation. Studies have shown that the use of ground beetle not only helps to regulate blood lipids and oxygen free radicals but also has anticoagulant, antithrombotic, and antioxidant free radical effects and protects vascular endothelial cells [38,39]. *Rhizoma chuanxiong* can dilate coronary arteries, increase coronary blood flow, improve myocardial ischemia and hypoxia, as well as inhibit atherosclerosis

and platelet aggregation [40,41]. Peach kernel has obvious anticoagulant, anti-platelet aggregation, and hemorheology-ameliorative effects [42–44]. Cassia twig warms the meridians and helps *yang* transform *qi*. Studies have found that the use of cassia twig can promote vasodilation and has analgesic, anti-inflammatory, and anti-allergic effects [45,46]. Dried *Radix rehmannia* clears away heat, promotes fluid, and cools blood for hemostasis. A study has found that dried *Radix rehmannia* can inhibit the release of vascular endothelin and improve microvascular blood circulation [47].

In this study, we aimed to objectively evaluate the efficacy and safety of the *Tongxin* formula in the treatment of CMVD through a randomized, double-blind, placebo-controlled clinical study. We reviewed D-SPECT images, measured scores pertaining to TCM symptoms, angina symptoms, and quality of life, and recorded adverse cardiovascular events and adverse reactions to evaluate treatment efficacy and safety, offering new strategies and methods for the prevention and treatment of CMVD using TCM, discussing the possible mechanism of the treatment of coronary microvascular disease was also discussed.

In this study, it was found that in terms of improving myocardial blood perfusion, the change of CFR level in the treatment group (CFR >2) was significantly higher than that in the control group ($P < 0.001$), and the improvement of left ventricular diastolic function in the treatment group (PFR >2.5) was significantly higher than that in the control group (73 % vs 47.4 %, $P = 0.024$), the difference was statistically significant. Studies have found that CFR <2 is an independent predictor of cardiovascular adverse events [48], indicating that Tongxin decoction can significantly improve CFR and left ventricular diastolic function in patients with coronary microvascular disease, thereby improving myocardial blood perfusion and myocardial ischemia.

At present, the treatment of CMVD in Western medicine is based on the treatment of coronary heart disease, mainly from the management of potential risk factors, anti-atherosclerosis, anti-angina pectoris, anti-platelet aggregation and improvement of myocardial ischemia. Qin Xiaofei et al. [49] confirmed that combined use of Shexiang Tongxin dropping pills on the basis of conventional western medicine had a significant effect on improving coronary blood flow reserve and quality of life compared with Western medicine alone. The study results showed that CFR >2 was 29.1 % in the treatment group after treatment, but there was no statistical significance in improving the incidence of major cardiovascular events. Other studies [25] have shown that ivabradine can reduce heart rate and myocardial oxygen consumption by blocking the SA node current, thereby increasing CFR. In this study, the proportion of CFR >2 in the treatment group after treatment was more than 90 %, and the results of this study showed that Tongxin formula could reduce the occurrence of cardiovascular adverse events and reduce the rate of repeated hospitalization, which has a good advantage in improving the prognosis of CMVD patients. It is considered that it may be related to the use of a large number of drugs for promoting blood circulation and removing blood stasis in Tongxin prescription used in this study. Relevant pharmacological studies have shown that drugs for promoting blood circulation and removing blood stasis, especially those with Astragalus, Chuanxiongxiong, Tuya and peach kernel as the core, have effects on improving microvascular function, myocardial ischemia and hypoxia, and vascular endothelial function [50–52]. In addition, drugs that promote blood circulation and remove blood stasis can also improve hemodynamics by dilating coronary arteries and peripheral vessels, thereby reducing vascular resistance and increasing myocardial blood perfusion [53].

In terms of improving clinical symptoms and quality of life, Seattle Angina Pectoris Scale is an effective and very reliable scale that can be used to evaluate clinical symptoms of patients with coronary heart disease [54], and TCM symptom score and angina pectoris symptom score are important indicators used to evaluate the efficacy of TCM symptoms. The results of this study showed that the total effective rate of TCM symptoms, angina pectoris symptoms and SAQ standard scores in the treatment group were higher than those in the control group ($P < 0.001$), indicating that Tongxin can improve the clinical symptoms and quality of life of CMVD patients. The study of Yue Ji et al. [55] showed that combined use of nicodil on the basis of conventional anti-angina medication could significantly improve the cardiac function and repeated hospitalization rate of CMVD patients, and the study results showed that the total effective rate of the nicodil treatment group was 80.9 %. Other relevant studies [56,57] showed that, Combined with Zhishi Xiebai Guizhi Decoction, Xinbao Pill, Tongxinluo and other drugs on the basis of conventional western medicine treatment, the clinical effect is more significant than that of simple Western medicine treatment. In this study, the total effective rate of TCM symptoms and angina pectoris in the Tongxin prescription treatment group after 6 months of follow-up was 89.1 % and 97.3 %, respectively, which was higher than previous studies and may be related to the following aspects: First, the specific assessment indicators of clinical efficacy are different. In previous studies, some clinical efficacy assessment indicators are mainly based on electrocardiogram changes before and after treatment, and some are mainly based on angina pectoris symptom improvement. Different evaluation indicators lead to different clinical efficacy. Second, the different TCM syndrome types of the enrolled patients or the different clinical effects caused by the individual differences of patients; Third, considering that Tongxin formula selected in this study may have better efficacy in improving coronary microcirculation and myocardial ischemia and hypoxia compared with previous studies.

Tongxin decoction used in this study is composed of Buyang Huanwu Decoction, Xuefu Zhuyu Decoction and Gualou Xiebai Guizhi Decoction. Studies have shown that Buyang Huanwu Decoction can inhibit platelet aggregation and release, inhibit platelet activation, improve vascular endothelial function and reduce lipid by increasing the content of cyclic adenosine phosphate in platelets. In addition, Buyang Huanwu Decoction can also remove oxygen free radicals. Play a role in improving coronary microcirculation and myocardial ischemia and hypoxia [58–61]. Xuefu Zhuyu Decoction has been used for the treatment of cardiovascular diseases for a long time since ancient times, especially for various blood stasis syndrome with good efficacy. Existing research results also confirm that Xuefu Zhuyu Decoction can inhibit inflammation, inhibit platelet aggregation, inhibit atherosclerosis, protect cardiomyocytes, improve vascular endothelial function and other functions [62,63]. Therefore, the Tongxin prescription treatment group in this study can significantly improve the clinical symptoms and quality of life of patients with CMVD, which may be related to the cardiovascular protective mechanism played by these drugs. Finally, in terms of drug safety, liver and kidney function impairment, drug allergy and other serious adverse reactions were not observed in both groups before and after treatment, and there were no significant changes ($P > 0.05$), suggesting that Tongxin formula has a good safety.

5. Conclusion

In conclusion, our study has underscored the significant potential of the *Tongxin* formula combined with conventional western medicine treatment to enhance coronary blood flow reserve, mitigate the occurrence of cardiovascular adverse events, ameliorate clinical symptoms, and enhance the overall quality of life among patients afflicted with CMVD. Of notable significance, this therapeutic intervention has exhibited superior efficacy when compared to the utilization of Western medicine in isolation. These compelling findings warrant the integration of the *Tongxin* formula as a valuable therapeutic modality within the comprehensive care framework for individuals grappling with CMVD.

This outcome provides a robust foundation for further exploration into the specific mechanisms of action underpinning the *Tongxin* formula's efficacy in CMVD treatment. Future investigations, including pertinent animal experiments, are imperative to elucidate the precise mechanisms governing its therapeutic effects. Simultaneously, given the limited clinical evidence pertaining to isolated qi deficiency and blood stasis, coupled with the prominence of accompanying symptoms, future studies necessitate expanded sample sizes to refine research pertaining to relevant TCM symptoms. This endeavor will also help validate whether the *Tongxin* formula confers similar benefits across various TCM symptom profiles associated with CMVD.

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Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by Ethics Committee of the Shanghai Municipal Hospital of Traditional Chinese Medicine (No.2020SHL-KY-27). Written informed consent was obtained from all participants.

Clinical trial Registration

www.chictr.org.cn/index.aspx, identifier: ChiCTR1900026799, 2019-10-22.

Availability of data and material

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Feng-Qun Xie: Writing – review & editing, Supervision, Formal analysis, Data curation. **Yi-Sheng Wang:** Writing – review & editing, Validation, Software, Formal analysis. **Lei Zhang:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **Wen Zhu:** Writing – review & editing, Visualization, Formal analysis, Data curation, Conceptualization. **Jie Cheng:** Writing – review & editing, Validation, Investigation, Conceptualization. **Yun-Yan Lu:** Writing – review & editing, Supervision, Methodology, Investigation. **Shao-Hua Xu:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis. **Xian-Kai Li:** Writing – review & editing, Project administration, Formal analysis, Data curation, Conceptualization. **Qi-Mao Feng:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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